In the two positive studies described above [4,6], the use of adjuvant cisplatin/vinorelbine was associated with significant toxicity (severe neutropenia [grade 3/4] in > 80% of patients and febrile neutropenia in > 8-10% of patients) and only few patients could receive treatment as scheduled. Therefore, the schedule of administration of vinorelbine of these studies is not routinely used. Nevertheless, it is possible that if vinorelbine was given by the more widely used schedule (days 1 and 8 every 3 weeks) it may have been more active.

Currently, the available evidence suggests that the best candidates for adjuvant therapy are those patients who have undergone lobectomy, those who have made a complete recovery from surgery, have no severe comorbidities, are aged < 70 years and have a performance status of 0 or 1. Two further issues that need to be addressed in future research are the potential differences in survival between smokers and never smokers, and the effect on prognosis of the absence or presence of vascular invasion. It is becoming clear that tumors in non-smokers differ from those in smokers in terms of histology and possibly prognosis. This could have implications for the risk of recurrence and hence the value of adjuvant therapy. Similarly, the presence or absence of vascular invasion may influence the risk of recurrence and hence whether adjuvant therapy is likely to be beneficial.

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Y1-12 **Young Investigators Day, Sat, Sept 1, 08:30 - 16:40**

What are the critical questions in the thoracic adjuvant radiotherapy: evolution from PORT

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Studies of postoperative irradiation show that it does not improve results in patients who have no evidence of metastasis to the hilar or mediastinal lymph nodes. In fact, postoperative irradiation might have a net deleterious effect on survival according to the post operative radiation therapy (PORT) meta analysis. Shields observed that local recurrence was infrequent in the case of a pathologically complete resection with no evidence of regional lymph node metastasis, so irradiation would accomplish little for such patients. Moreover, radiation therapy may place an additional burden on pulmonary function, especially in patients who have required pneumonectomy. A meta-analysis reiterated the long-recognized potential for adverse effects of radiation therapy when rigorous CT-based treatment planning is not done.

Several retrospective studies have suggested that postoperative irradiation can improve outcome when mediastinal nodal metastases are present. An analysis of postoperative radiation therapy in available prospective trials, most of which was not based on CT planning, showed neither a detrimental nor a beneficial effect. On the basis of the striking improvement in local control of squamous cell carcinoma shown by the Lung Cancer Study Group, the Eastern Cooperative Oncology Group (ECOG) coordinated a large intergroup trial to compare postoperative radiation therapy plus concurrent chemotherapy with cisplatin and etoposide to postoperative radiation therapy alone. In initial results for 373 patients eligible for analysis and a median follow-up of 44 months, the median survival was 42 months for patients given only radiation and 38 months for those given combined-modality treatment (P = 0.48). No significant differences were found in failure patterns between the 2 study groups. Therefore, although postoperative irradiation can clearly reduce the risk of local recurrence in patients with mediastinal node metastasis, its effect on survival (with or without adjuvant chemotherapy) is still under investigation.

Finally, Sawyer and others studied patients with stage IIIA (N2) NSCLC using regression tree analysis to identify patients at low, intermediate, and high risk of local recurrence. Numbers of involved lymph nodes, locations of mediastinal lymph nodes relative to the location of the primary tumor, and T stage were used to identify intermediate- and high-risk groups. Excluding the low-risk group, postoperative radiation therapy conferred a highly significant improvement in local recurrence-free and overall survival rates. This approach can form the basis for future studies of the value of postoperative irradiation and chemotherapy.

Controversy continues regarding the most effective treatment for patients with marginally resectable NSCLC. A retrospective review of patients treated at The University of Texas M. D. Anderson Cancer Center confirmed the impression that patients with more favorable disease are selected for surgical intervention. Two small prospective studies provided quite similar results suggesting that induction chemotherapy improves survival in patients with resectable NSCLC. Important aspects of post-operative radiotherapy are patients selection

(N2 NSCLC and lobectomy patients rather than pneumonectomy patients). Those patients with N2 NSCLC who require pneumonectomy should be treated by chemoradiotherapy to avoid lung toxicity. Careful CT/PET based post-pretaive radiotherapy is essential to target positive mediastinal nodes without irradiating residual lung . Now we are able to SPECT to find the part of the functional lung where irradiation needs to be avoided. If there was microscopic positive margin left, post operative radiotherapy needs to be given with minimal 60 Gy in 30 fractions and concurrent cisplatin based chemotherapy. For the negative margin and N2 patients, 50 Gy in 25 fractions will be given with conformal radiation therapy technique. The lung heterogeneity correction should be considered as well as dose volume histogram. The lung volume needs to be lea than 40 % at V20 if post-operative radiotherapy will be given. If concurrent chemoradiotherapy is required because of the positive margins, V20 should be less than 35% to avoid treatment related pneumonitis. These patients with microscopic N2 disease might live long enough to manifest cardiac toxicity. Therefore avoidance of the large volume cardiac irradiation is also essential among patients who already have high risk of cardiovascular disease due to smoking. Because of the mediastinal nodal irradiation, not all patients need 4DCT.

Future investigation is required to find which modality (adjuvant chemotherapy vs. radiotherapy) needs to be given immediately after surgery for those with N2 disease and negative margin.

Y1-13 **Young Investigators Day, Sat, Sept 1, 08:30 - 16:40**

Assessment of mediastinal disease: invasive approach vs PET: the case for invasive techniques

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Accurate staging of the mediastinum in non-small cell lung cancer is essential to appropriately determine if patients should be candidates for surgical resection, neo-adjuvant therapy, or for definitive chemoradiation. It has been shown that patients with persistent, bulky N2 disease following induction therapy have poor survival if they go on to surgery. Thus, re-staging patients after induction therapy is becoming even more important; however, the ideal method of staging the mediastinum is still under debate. With the continued development of new minimally invasive techniques, such as endobronchial ultrasound (EBUS) guided transbronchial needle biopsy and VATS staging, the question is sure to evolve.

Mediastinoscopy.

Cervical mediastinoscopy is the current gold standard for mediastinal staging. Pooling data from several studies, Toloza et al, found that cervical mediastinoscopy had a sensitivity of 81% and specificity approaching 100%; for a positive predictive value of 1.0 and negative predictive value of 0.91.1 In contrast, PET had an overall positive predictive value of 0.79 and negative predictive value of 0.93.2 The main risk with PET is that some patients with pathologically negative mediastinal disease may continue to have FDG-avid lymph nodes. Thus, some patients with potentially curable disease will be denied surgical intervention. Standard cervical mediastinoscopy is not able to sample aortopulmonary window, paraesophageal, and pulmonary ligament nodes. Other drawbacks include the need for general anesthesia, the risk of bleeding, and risk of recurrent laryngeal nerve injury.

Chamberlain Procedure and Video-Assisted Thoracic Surgery (VATS)

A left anterior parasternal mediastinotomy, or Chamberlain procedure, provides access to the subaortic space, however, generally requires division of costal cartilage. The sensitivity and specificity are 74% and 100% respectively. VATS also allows sampling of the AP window nodes. If performed at the time of definitive resection, an initial VATS sampling of ipsilateral mediastinal lymph nodes with frozen section may prevent the surgeon from going on to perform an unnecessary resection. There have been relatively little data comparing the accuracy of VATS staging to either PET or conventional mediastinoscopy. Like mediastinoscopy, these procedures require general anesthesia and carry a risk of bleeding.

Endoscopic and endobronchial ultrasound.

Endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) allows access to left sided paratracheal nodes, as well as para-aortic, subcarinal, para-esophageal, and sometimes inferior pulmonary ligament nodes. For these lymph nodes, EUS-FNA has been shown to have comparable sensitivity and specificity to CT and PET. The diagnostic accuracy is further increased if there is lymph node enlargement. Endobronchial ultrasound (EBUS) is a relatively newer method of staging that uses an ultrasound transducer mounted on a videobronchoscope to guide FNA. It can be used to biopsy paratracheal, subcarinal, and peribronchial nodes; in experienced hands, even some AP window nodes can be biopsied safely. In the few published case series, the sensitivity and specificity are roughly 85% and 100% respectively. Both EUS and EBUS can be done relatively quickly, without general anesthesia, and with a minimal complication rate. Combined, EUS and EBUS have the potential to accurately stage the entire mediastinum with low morbidity.

Overview

The role for invasive staging of the mediastinum continues to evolve as new technologies emerge. Randomized trials comparing the newer methods with established methods are necessary. Although it is yet unclear which method or methods will become the new standard, all these invasive approaches have one distinct advantage over non-invasive methods like CT or PET - access to tissue. For patients with mediastinal disease, these procedures can be used to make a definitive tissue diagnose at the same time as staging, which is required for initiation of induction therapy. In addition, as molecular profiling of tumors becomes more important, being able to analyze the biology of the tumor (both pre- and post-induction) may add another dimension to individually tailored treatment regimens.

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Y1-14 **Young Investigators Day, Sat, Sept 1, 08:30 - 16:40**

Hurdles in the Development of a New Drug

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Investigations of novel agents remain a cornerstone of clinical research in Oncology. Guidelines for investigations of novel agents have existed for many years. They include sequential investigations of a novel agent in the phase I, II and III setting. It is clear that the classical phase II study design is not particularly well suited to investigations of targeted agents since it may not result in measurable objective responses. Alternative trial designs have been investigated over recent years. These include a randomized phase II trials as well as randomized discontinuation trials and dose range trials. Examples of such studies and their impact on recent drug development will be presented.

Y1-15 **Young Investigators Day, Sat, Sept 1, 08:30 - 16:40**

Career choices: options in academia, private practice, industries and government

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A Medical Doctor studies for longer than most any other profession. The reason for this is that there is a considerable amount of knowledge required in order to be able to provide a correct diagnosis and cure to patients in his area of speciality. If diagnostic part of his activity is directly related to clinical practice (academic and/or private), the implementation of this activity requires a medically driven/controlled administrative organization. The dramatic improvement, technicality, cost and specificity of diagnostic procedures make the role of a single physician less and less predominant and the need for regulation more and more important. A medical input is necessary to determine which procedures are the most appropriate and should be available for all patients.

